REMARKS

Claims 1-17 and 19 are pending in the application. Claims 1-7 and 9-11 stand withdrawn from consideration. Claims 13-16 have been deleted and new Claims 20 and 21 have been added. Amended Claims 8, 12, 17, and 19 stand rejected. Applicants address the rejections in the order in which they were presented in the office action.

DRAWING OBJECTION

The office action has objected to Figure 2A. Submitted herewith for approval are proposed amended drawing sheets for Figure 2A. Applicants have renumbered the three sheets of originally filed Figure 2A as Figure 2A, 2B and 2C, and the one sheet of originally filed Figure 2B as Figure 3. The BRIEF DESCRIPTION OF THE DRAWINGS section of the specification has been amended to indicate the renumbering of the figures. On amended Figure 2B, Applicants have corrected the typographical error for the term "aliphatic." Also on amended Figure 2B, Applicants have amended the definition of R''' to read "small or branched aliphatic like side chain of Leu, Val, Ile, or Ala." Support for this amendment is found in the drawings of the priority document Israel Patent Application No. 118657 filed June 14, 1996, a copy of which is attached at Tab A. The terms "Etc." have also been deleted in amended Figure 2C. A copy of the originally filed Figure 2A and 2B showing the above-identified changes in red ink can be found in the Appendix filed concurrently herewith. Applicants respectfully request approval of the amendments to these drawings. Upon approval of these changes, corrected drawings will be submitted to the Official Draftsperson of the United States Patent and Trademark Office.

35 U.S.C. §112, FIRST PARAGRAPH REJECTION OF CLAIMS 8, 12-17 AND 19

The Examiner has rejected Claims 8 and 12-17, and 19 under 35 U.S.C. §112, first paragraph, on the grounds that they describe a process for which neither the time nor the conditions to achieve the intended result are disclosed by the specification. Applicants have deleted Claims 13-16 and amended Claims 8, 12, 17, and 19 as suggested by the Examiner. Therefore, Applicants respectfully request that the Examiner withdraw his 35 U.S.C. §112, first paragraph rejections regarding this issue for Claims 8, 12, 17, and 19.

Additionally, the Examiner has rejected Claims 8, 12-17 and 19 under 35 U.S.C. §112, first paragraph on several grounds in that they contain subject matter which was not described

in the specification in such a way as to reasonably convey to one skilled in the art that the inventors possessed the claimed invention. The Examiner's first ground for this rejection has been addressed because the Applicants have deleted Claims 13-16. The Examiner's second ground for this rejection has been addressed in that Claims13-16 have been deleted and Claims 8, 12, 17, and 19 have been amended by removing "H" as an option for "Z".

The Examiners third ground for this rejection addresses "Y" and "Y'" as hydroxyl. Applicants have amended Claim 8. Applicants have canceled Claim 18 and amended Claims 8, 17, and 19 to address the Examiners concerns and added Claim 21 as suggested by the Examiner. No new matter has been added.

35 U.S.C. §112, SECOND PARAGRAPH REJECTION OF CLAIMS 8, 12-17 AND 19

Next, the Examiner rejected Claims 8, 12-17, and 19 under 35 U.S.C. §112, second paragraph, for failing to point out and distinctly claim what the Applicants believe to be their invention. Applicants have deleted Claims 13-16 and amended Claims 8, 12, 17, and 19 to adopt the Examiner's suggested language as discussed in an Examiner Interview. Therefore, the Applicants respectfully request that the Examiner remove this rejection.

The Examiner further rejects Claims 12, and 13-16 under 35 U.S.C. §112, second paragraph. Applicants have deleted Claims 13-16 and amended Claim 12 to correct any lack of antecedent basis. Therefore, Applicants respectfully request that the Examiner remove these rejections.

The Examiner also objected to Claims 8, 17, and 19 because they recite "Y" and "Y'" as a "keto, carbamido, sulfoxide, alkylsulfonyl, and sulfone." Applicants have amended Claims 8, 17 and 19 to address the Examiner's concern by providing additional bonding groups for these functional groups. No new matter has been added. Applicants respectfully request that the Examiner remove this rejection.

35 U.S.C. §102 (b) REJECTION OF CLAIMS 8, 12, 17 AND 19

The Examiner rejected Claims 8, 17 and 19 under 35 U.S.C. §102(b) as being anticipated by Berger, U.S. Patent 3,657,436 (the '436 patent). Under the same statute, the Examiner rejected Claims 8, 12, 17 and 19 as being anticipated by Singh, *Tetrahedron Letters*, 32:5279 (1991).

Berger, U.S. Patent 3,657,436

The Examiner rejected Claims 8, 17 and 19 under 35 U.S.C. §102(b) as being anticipated by Berger, U.S. Patent 3,657,436 (the '436 patent). Applicants have amended Claim 8 in view of the Examiner interview and removed the possibility of R_1 being hydroxyl. Applicants respectfully disagree with the Examiner asserting Berger against Claims 17 and 19 because R_1 is not a hydroxyl in these claims. For these reasons, Applicants respectfully request that the Examiner withdraw this 35 U.S.C. §102(b) rejection of Claims 8, 17 and 19 in view of Berger.

Singh, Tetrahedron Letters 32:5279-5282 (1991)

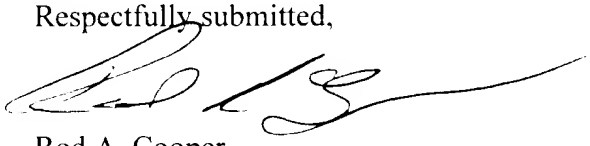
On a final note, the Examiner rejected Claims 8, 12, 17 and 19 under 35 U.S.C. §102(b) as being anticipated by Singh, et al. *Tetrahedron Letters* 32:5279-5282 (1991) (Singh). Applicants have amended Claims 8, 12, 17 and 19 by removing the possibility of "Z" being hydrogen. As indicated in the Examiner Interview, such an amendment would overcome this rejection. Therefore, Applicants respectfully request that the Examiner withdraw this 35 U.S.C. §102(b) rejection of Claims 8, 12, 17 and 19 in view of Singh.

CONCLUSION

For reasons delineated above, Applicants respectfully request the consideration of all pending claims and proposed drawings, and favorable action on the same.

Applicants do not believe that any additional fees are necessary for filing this amendment. However, if this is in error, please deduct the necessary fees from the Sidley Austin Brown & Wood LLP Deposit Account No. 18-1260.

Respectfully submitted,



Rod A. Cooper
Registration No. 42,436

RAC/KLK/ld
May 17, 2002
SIDLEY AUSTIN BROWN & WOOD LLP
717 N. Harwood, Suite 3400
Dallas, Texas 75202
(214) 981-3331

APPENDIX: VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

At Page 17, line 3:

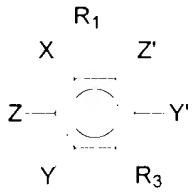
FIG. 2A, 2B and 2C give [gives] examples of peptidomimetic moeities for R_1; and

At Page 17, line 4:

FIG. [2B] 3 gives examples of compound of the present invention with a peptidomimetic moeity.

IN THE CLAIMS

8. (Four time amended) A method of inhibiting [picornaviral replication in a subject] picornavirus activity, comprising [the step of administering an effective amount of] contacting the picornavirus with a compound [having a] of the formula:



wherein

X is selected from the group consisting of C=O, S=O, C=S, (C=O)–NH, (C=O)–O and (C=O)–S:

R_1 is selected from the group consisting of:

(i) hydrogen[, hydroxyl] or a hydrocarbon chain from 1 to about 10 carbons long selected from the group consisting of saturated, unsaturated and fluorinated, wherein said hydrocarbon chain is unsubstituted or substituted with at least one R^{11}, wherein R^{11} is selected from the group consisting of:

(ia) C_1-C_4 alkyl, C_2-C_4 alkenyl, C_3-C_8 cycloalkyl, C_6-C_{10} bicycloalkyl or aryl which may be substituted or unsubstituted;

(ib) halogen, cyano, nitro, amino, hydroxy, adamantyl, carbamyl, carbamyloxy or keto;

(ic) an oligopeptide of 1-3 amino acid residues; and

(id) $NR^{13}R^{14}$, CO_2R^{13}, $O(C=OR^{13})$, SO_2R^{14}, SOR^{14}, $(C=O)NR^{13}R^{14}$, or $NR^{14}(C=O)R^{13}$;

wherein:

R^{13} is selected from the group consisting of hydrogen, phenyl, benzyl, C_1-C_6 alkyl and C_3-C_6 alkoxyalkyl; and

R^{14} is selected from the group consisting of hydrogen, hydroxyl, and benzyl;

(ii) an oligopeptide or peptidomimetic molecule of 1 to 5 amino acids;

(iii) C_3-C_6 cycloalkyl, C_6-C_{10} bicycloalkyl, C_3-C_7 cycloalkylmethyl, or C_7-C_{10} arylalkyl, which may be additionally substituted with R^{11} as defined above;

R_3 is selected from the group consisting of:

(i) hydrogen, phenyl, hydroxyl, C_1-C_{12} hydrocarbon chain or O-C_1-C_{12} hydrocarbon chain which may be additionally substituted with at least one R^{11} as defined above; and

(ii) an oligopeptide of 1 to 3 amino acids joined to the backbone by an oxygen or a peptidomimetic;

Z is selected from the group consisting of [hydrogen,] hydroxyl, sulfhydryl, carboxyl and NHR^{11}, wherein R^{11} is defined as above;

Z' is selected from the group consisting of:

(i) hydroxyl, amino, [carbamid] carbamido, carbamyl, carbamyloxy or halogen;

(ii) hydrogen; and

(iii) C_1-C_4 alkyl, [C_1-C_4] C_2-C_4 alkenyl, C_3-C_7 cycloalkenyl, or C_1-C_3 alkoxy which may be additionally substituted with at least one R^{11} as defined above;

alternatively Z' and R_1 collectively form a ring system selected from the group consisting of:

(a) C_5-C_8 carbocyclic ring which may be saturated or unsaturated, and which may be additionally substituted with at least one R^{11} as defined above; and

(b) C_5-C_{10} heterocyclic ring system which may be saturated or unsaturated and which includes at least one nitrogen, oxygen or sulfur atom, and which may be additionally substituted with at least one R^{11} as defined above;

Y and Y' are independently selected from the group consisting of:

(i) hydrogen, halogen, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

(ii) carbamyl, [carbamide] carbamido, cyano, [keto] COR^{11}, vinyl, [sulfoxide], nitro, [C_1-C_3 alkylsulfonyl] SO_2R^{11}, or [sulfone] SOR^{11} wherein R^{11} is defined above;

(iii) C_1-C_3 alkyl which may be additionally substituted with at least one R^{11} as defined above;

(iv) an oligopeptide or a peptidomimetic of 1 to 3 amino acids; and

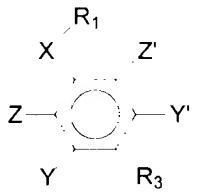
(v) Y' may additionally be hydroxyl;

and pharmaceutically acceptable salts thereof; with the proviso that when X-R_1 is a fluorinated keto acyl, Z is hydrogen;

for a time and under conditions effective to [effectively] inhibit [picornaviral] replication of said picornavirus.

12. (Thrice amended) A method according to claim 8, wherein [the] said picornavirus [species] is a rhinovirus.

[13. A method for inhibiting picornaviral replication in a subject, wherein said compound has the formula:



wherein X is –C=O;

R_1 is $–CF_3$;

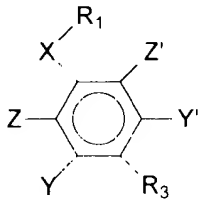
Z and Z′ are hydroxyl, except when X-R_1 is a fluorinated keto acyl group, Z must be hydrogen;

R_3 is hydrogen; and

Y and Y′ are selected from the group consisting of –Cl, –I, –Br, $–CF_3$, –F, –CN, –COOH, $–SO_3H$, $–SO_2NH_2$ and $–CONH_2$

to effectively inhibit picornaviral replication.]

[14. A method for inhibiting picornaviral replication in a subject, wherein said compound has the formula:



wherein X is –C=O;

R_1 is $–CF_3$;

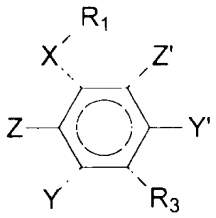
Z is hydroxyl, except when X-R_1 is a fluorinated keto acyl group, Z must be hydrogen;

Z′ and R_3 are hydrogen; and

Y and Y′ are selected from the group consisting of –Cl, –I, –Br, $–CF_3$, –F, –CN, –COOH, $–SO_3H$, $–SO_2NH_2$ and $–CONH_2$

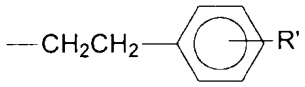
to effectively inhibit picornaviral replication.]

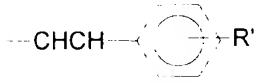
[15. A method for inhibiting picornaviral replication in a subject, wherein said compound has the formula:

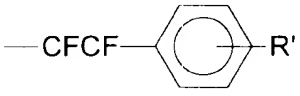


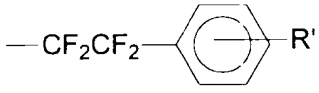
wherein X is –C=O;

R_1 is H, $–CH_3$, $–CF_3$, $CH_3–CH_2–CH_2–CH_2–CH_2–$, $CH_3–CH_2–$, $CH_3–CH_2–CH_2–$, $CF_3–CF_2–CF_2–CF_2–CF_2–$, –NH–R′′or one of the following phenyl groups









wherein R′ is –OH, $–NH_2$, –COOH, or $–COCH_3$ and R′′ is –OH, $–NH_2$, $–OCH_3$ or $–OCH_2CH_3$;

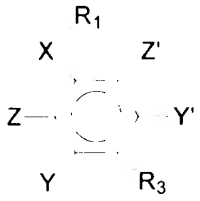
Z and Z′ are hydroxyl, except when X-R_1 is a fluorinated keto acyl group, Z must be hydrogen;

R_3 is hydrogen; and

Y and Y′ are $-CF_3$

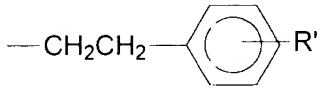
to effectively inhibit picornaviral replication.]

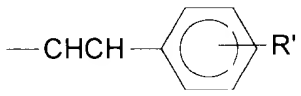
[16. A method for inhibiting picornaviral replication in a subject, wherein said compound has the formula:

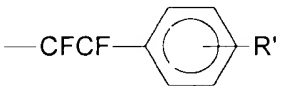


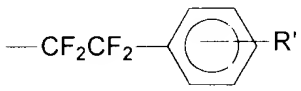
wherein X is –C=O;

R_1 is H, $-CH_3$, $-CF_3$, $CH_3-CH_2-CH_2-CH_2-CH_2-$, CH_3-CH_2-, $CH_3-CH_2-CH_2-$, $CF_3-CF_2-CF_2-CF_2-CF_2-$, –NH–R′′, or one of the following phenyl groups









wherein R′ is –OH, $-NH_2$, –COOH, or $-COCH_3$ and R′′ is –OH, $-NH_2$, $-OCH_3$ and $-OCH_2CH_3$;

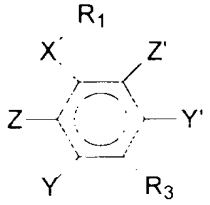
Z is hydroxyl, except when X-R_1 is a fluorinated keto acyl group, Z must be hydrogen;

Z′ and R_3 are hydrogen; and

Y and Y′ are $-CF_3$

to effectively inhibit picornaviral replication.]

17. (Thrice amended) A method of inhibiting [picornaviral replication in a subject, wherein said method comprises the use of] picornavirus activity, comprising contacting the picornavirus with a compound [with] of the formula:



wherein X is selected from the group consisting of –C=O-, –S=O-, and –C=S-;

R_1 is selected from the group consisting of:

(i) a hydrocarbon chain which may be unsubstituted or substituted with at least one R^{11}, wherein R^{11} is selected from the group consisting of:

(ia) C_1-C_4 alkyl, C_2-C_4 alkenyl, C_3-C_8 cycloalkyl, C_6-C_{10} bicycloalkyl or aryl which may be substituted or unsubstituted;

(ib) halogen, cyano, nitro, amino, hydroxy, adamantyl, carbamyl, carbamyloxy or keto;

(ic) an oligopeptide of 1-3 amino acid residues; and

(id) $NR^{13}R^{14}$, COR^{13}, $O(C=OR^{13})$, SO_2R^{14}, SOR^{14}, $(C=O)NR^{13}R^{14}$, or $NR^{14}(C=O)R^{13}$;

wherein:

R^{13} is selected from the group consisting of hydrogen, phenyl, benzyl, C_1-C_6 alkyl, and C_3-C_6 alkoxyalkyl; and

R^{14} is selected from the group consisting of hydrogen, hydroxyl, and benzyl;

R_3 is selected from the group consisting of:

(i) phenyl, hydroxyl, C_1-C_{12} hydrocarbon chain and O—C_1-C_{12} hydrocarbon chain which may be additionally substituted with at least one R^{11} as defined above; and

(ii) an oligopeptide or a peptidomimetic molecule of 1 to 3 amino acids, joined to the backbone by an oxygen;

Z is selected from the group consisting of [hydrogen,] hydroxyl, sulfhydryl, carboxyl, and NHR^{11}, wherein R^{11} is defined as above;

Z′ is selected from the group consisting of:

(i) hydroxyl, amino, carbamido, carbamyl, carbamyloxy, and halogen;

(ii) C_1-C_4 alkyl, [C_1-C_4] $\underline{C_2\text{-}C_4}$ alkenyl, C_3-C_7 cycloalkenyl and C_1-C_3 alkoxy which may be additionally substituted with at least one R^{11} as defined above;

Y and Y' are independently selected from the group consisting of:

(i) hydrogen, halogen, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

(ii) carbamyl, [carbamide] carbamido, cyano, [keto] $\underline{COR^{11}}$, vinyl, [sulfoxide], nitro, [C_1-C_3 alkylsulfonyl] $\underline{SO_2R^{11}}$, or [sulfone] $\underline{SOR^{11}}$, wherein R^{11} is defined above;

(iii) C_1-C_3 alkyl which may be additionally substituted with at least one R^{11} as defined above;

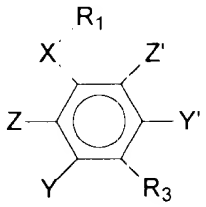
(iv) an oligopeptide or a peptidomimetic of 1 to 3 amino acids; and

(v) Y' may additionally be hydroxyl;

and pharmaceutically acceptable salts thereof; with the proviso that when X-R_1 is a fluorinated keto acyl, Z is hydrogen

for a time and under conditions effective to [effectively] inhibit [picornaviral] replication of said picornavirus.

19. (Twice amended) A method of inhibiting [picornaviral replication in a subject, wherein said method comprises the use of] picornavirus activity, comprising contacting the picornavirus with a compound [with] of the formula:



wherein X is selected from the group consisting of –C=O-, –S=O-, and –C=S-;

R_1 is selected from the group consisting of:

(i) a hydrocarbon chain which may be unsubstituted or substituted with at least one R^{11}, wherein R^{11} is selected from the group consisting of:

(ia) C_1-C_4 alkyl, C_2-C_4 alkenyl, C_3-C_8 cycloalkyl, C_6-C_{10} bicycloalkyl or aryl which may be substituted or unsubstituted;

(ib) halogen, cyano, nitro, amino, hydroxy, adamantyl, carbamyl, carbamyloxy or keto;

(ic) an oligopeptide of 1-3 amino acid residues; and

(id) $NR^{13}R^{14}$, COR^{13}, $O(C{=}OR^{13})$, SO_2R^{14}, SOR^{14}, $(C{=}O)NR^{13}R^{14}$, or $NR^{14}(C{=}O)R^{13}$;

wherein:

R^{13} is selected from the group consisting of hydrogen, phenyl, benzyl, C_1-C_6 alkyl, and C_3-C_6 alkoxyalkyl; and

R^{14} is selected from the group consisting of hydrogen, hydroxyl, and benzyl;

R_3 is selected from the group consisting of:

(i) phenyl, hydroxyl, C_1-C_{12} hydrocarbon chain and O—C_1-C_{12} hydrocarbon chain which may be additionally substituted with at least one R^{11} as defined above; and

(ii) an oligopeptide of 1 to 3 amino acids[, an oligopeptide of 1 to 3 amino acids] joined to the backbone by an oxygen or a peptidomimetic;

Z is selected from the group consisting of [hydrogen,] hydroxyl, sulfhydryl, carboxyl, and NHR^{11}, wherein R^{11} is defined as above;

Z′ is selected from the group consisting of:

(i) hydroxyl, amino, [carbamide] carbamido, carbamyl, carbamyloxy, and halogen;

(ii) C_1-C_4 alkyl, [C_1-C_4] C_2-C_4 alkenyl, C_3-C_7 cycloalkenyl and C_1-C_3 alkoxy which may be additionally substituted with at least one R^{11} as defined above;

Y and Y' are independently selected from the group consisting of:

(i) hydrogen, halogen, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

(ii) carbamyl, [carbamide] carbamido, cyano, keto, vinyl, sulfoxide, nitro, C_1-C_3 alkylsulfonyl, or sulfone;

(iii) C_1-C_3 alkyl which may be additionally substituted with at least one R^{11} as defined above; and

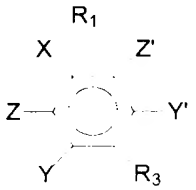
(iv) an oligopeptide or a peptidomimetic of 1 to 3 amino acids; [and

(v) Y' may additionally be hydroxyl;]

and pharmaceutically acceptable salts thereof; with the proviso that when $X–R_1$ is a fluorinated keto acyl, Z is hydrogen;

for a time and under conditions effective to [effectively] inhibit [picornaviral] replication of said picornavirus.

20. A method of inhibiting picornavirus activity, comprising contacting the picornavirus with a compound of the formula:



wherein

X is selected from the group consisting of C=O, S=O, C=S, (C=O)–NH, (C=O)–O and (C=O)–S:

R_1 is selected from the group consisting of:

(i) hydrogen or a hydrocarbon chain from 1 to about 10 carbons long selected from the group consisting of saturated, unsaturated and fluorinated, wherein said hydrocarbon chain is unsubstituted or substituted with at least one R^{11}, wherein R^{11} is selected from the group consisting of:

(ia) C_1-C_4 alkyl, C_2-C_4 alkenyl, C_3-C_8 cycloalkyl, C_6-C_{10} bicycloalkyl or aryl which may be substituted or unsubstituted;

(ib) halogen, cyano, nitro, amino, hydroxy, adamantyl, carbamyl, carbamyloxy or keto;

(ic) an oligopeptide of 1-3 amino acid residues; and

(id) $NR^{13}R^{14}$, CO_2R^{13}, $O(C=OR^{13})$, SO_2R^{14}, SOR^{14}, $(C=O)NR^{13}R^{14}$, or $NR^{14}(C=O)R^{13}$;

wherein:

R^{13} is selected from the group consisting of hydrogen, phenyl, benzyl, C_1-C_6 alkyl and C_3-C_6 alkoxyalkyl; and

R^{14} is selected from the group consisting of hydrogen, hydroxyl, and benzyl;

(ii) an oligopeptide or peptidomimetic molecule of 1 to 5 amino acids;

(iii) C_3-C_6 cycloalkyl, C_6-C_{10} bicycloalkyl, C_3-C_7 cycloalkylmethyl, or C_7-C_{10} arylalkyl, which may be additionally substituted with R^{11} as defined above;

R_3 is selected from the group consisting of:

(i) hydrogen, phenyl, hydroxyl, C_1-C_{12} hydrocarbon chain or O–C_1-C_{12} hydrocarbon chain which may be additionally substituted with at least one R^{11} as defined above; and

(ii) an oligopeptide of 1 to 3 amino acids joined to the backbone by an oxygen or a peptidomimetic;

Z is OH;

Z' is H;

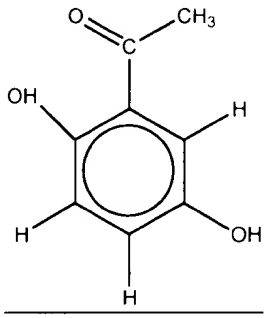
Y is H;

Y' is OH;

and pharmaceutically acceptable salts thereof;

for a time and under conditions effective to inhibit replication of said picornavirus.

21. A method of inhibiting picornavirus activity, comprising contacting the picornavirus with a compound of the formula:

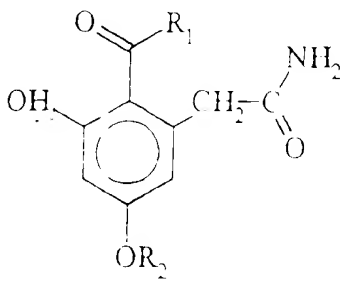


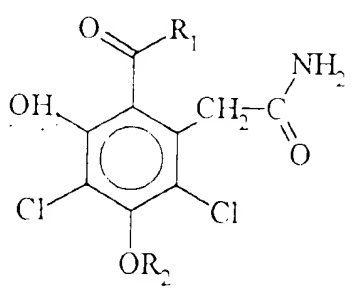
and pharmaceutically acceptable salts thereof for a time and under conditions effective to inhibit replication of said picornavirus.

IN THE DRAWINGS

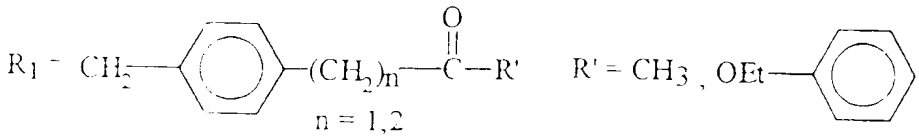
Attached are copies of originally filed Figure 2A and 2B with the proposed drawing changes marked in red ink.

Figure 2A

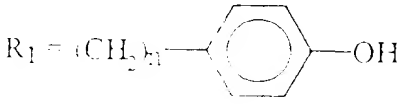




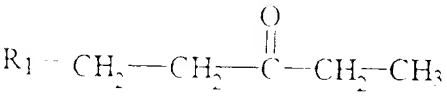
1

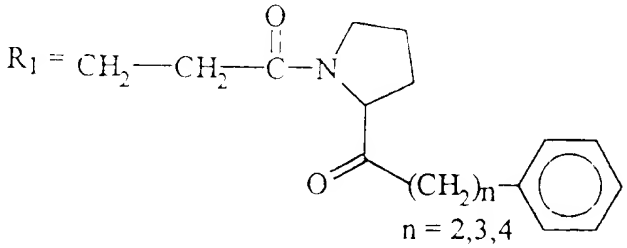


n = 1,2

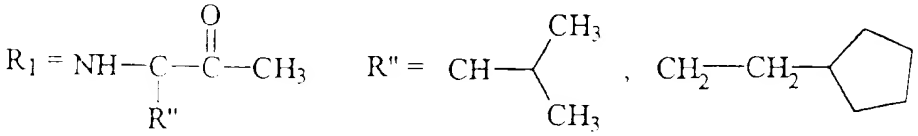


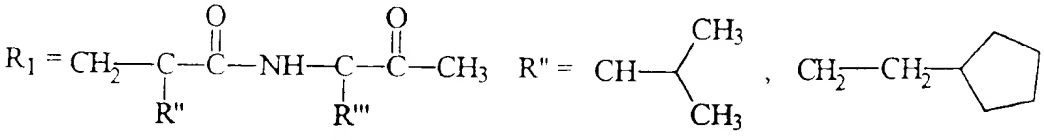
2





n = 2,3,4

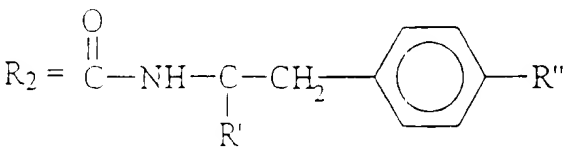


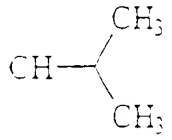


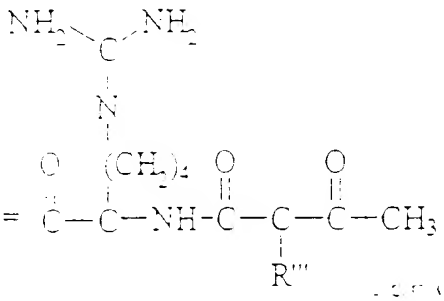
R''' = aromatic ring

Figure 2A (con't)

3.



R' =  , $CH_2—CH_3$, CH_3 , Or any branched aliphatic chain

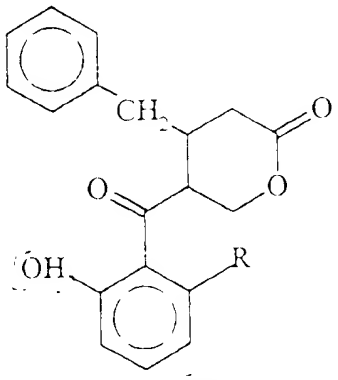


R''' = Small or branches aliphatic like side chain of Leu, Val, Ile

Figure 2A (con't)

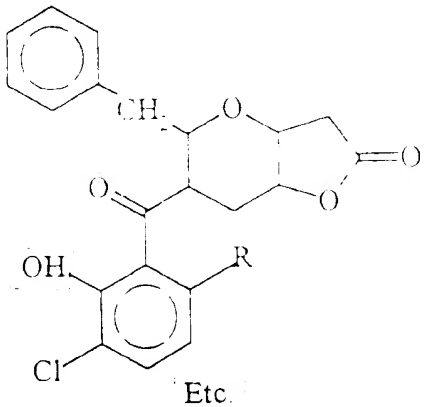
4

R_1 =



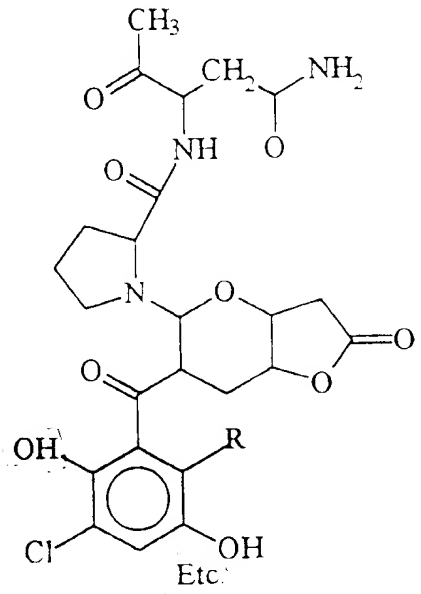
Etc.

R_1 =



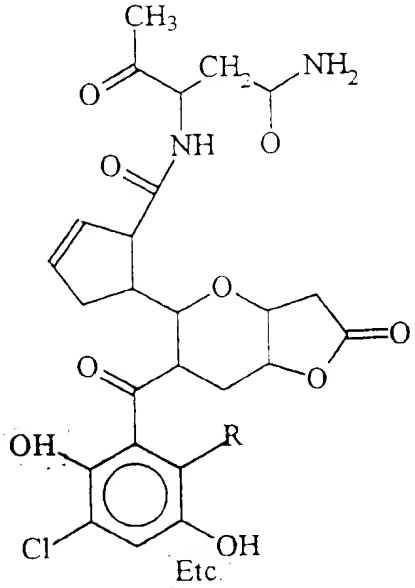
Etc.

R_1 =



Etc.

Or



Etc.

Figure 2B